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08/866,279	05/30/97	DYMECKI	S 234805

EXAMINER	
BAKER, A	
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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

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Office Action Summary

Application No.	Applicant(s)
08/866,279	Dymecki
Examiner	**Group Art Unit**
Anne-Marie Baker, Ph.D.	1632

☒ Responsive to communication(s) filed on *Aug 14, 2000*.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-49* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-49* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

The Appeal Brief filed on August 14, 2000 (Paper No. 21) has been entered into the record of this case. The arguments noted therein are addressed here.

Claims 1-49 are pending in the instant application.

The following rejections constitute the complete set of rejections being applied to the instant application. Rejections and objections not reiterated from the previous office action are hereby withdrawn

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-49 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification fails to provide an enabling disclosure for the claimed transgenic mice, the method of *in vivo* genetic engineering, or the system for genetic manipulation, because the phenotype of a transgenic mouse is unpredictable. The only use for the claimed invention is to produce functional recombination in a transgenic mouse such that a recombination-dependent phenotype is conferred to the claimed mouse as a result of gene activation or inactivation. While this is a credible utility, the instant specification does not teach how to produce functional recombination in the claimed mice. The specification envisions both gene activation and inactivation. However, in the absence of functional recombination, one skilled in the art would

not know how to use the claimed Flp recombinase transgenic mice and undue experimentation would have been required to determine how to used the claimed compositions and methods.

The specification fails to provide an enabling disclosure for the claimed transgenic mice because the specification does not teach how to produce functional recombination in mice carrying an Flp recombinase transgene and Flp recognition sequences. The specification does not offer adequate guidance for producing a transgenic mouse of the type claimed, wherein a transgene-dependent phenotypic alteration is produced. The mere capability to perform gene transfer in mice is not enabling for the claimed transgenic mice because the desired phenotype cannot be predictably achieved simply by introducing transgene constructs of the types recited in the claims. While gene transfer techniques are well-developed for a number of species, especially the mouse, methods for achieving the desired level of transgene expression in appropriate tissues are less well-established. The introduction of DNA into the mammalian genome can ordinarily be achieved most reliably by microinjection or retrovirus-mediated gene transfer. However, the state of the art for transgenics is unpredictable because the method of gene transfer typically relies on random integration of the transgene construct. Insertional inactivation of endogenous genes and position effects (see Wall, 1996, p. 61, paragraph 3) can dramatically influence the phenotype of the resultant transgenic animal. Integration of the transgene near highly active genes or, alternatively, in a transcriptionally inactive region, can influence its level of expression. Furthermore, expression of the transgene and the effect of transgene expression on the phenotype of the transgenic animal depends on the particular gene construct used, to an unpredictable extent. The particular genetic elements required for appropriate expression varies from species to species. Wall (1996) reports that our lack of understanding of essential genetic control elements makes it difficult to design transgenes with predictable behavior (p. 61, paragraph 3). Houdebine (1994) discloses that in the field of transgenics, constructs must be designed case by case without general rules to obtain good expression of a

transgene; for example, specific promoters, presence or absence of introns, etc. (p. 275, column 1, paragraph 1). Kappel et al. (1992) disclose the existence of inherent cellular mechanisms that may alter the pattern of gene expression such as DNA imprinting, resulting from differential CpG methylation (p. 549, column 2, 3rd full paragraph). The level of skill in the transgenic art is such that one cannot predict whether a transgene that is expressed in a mouse will also be expressed efficiently in another animal. For example, Strojek and Wagner (1988) pointed out that a high degree of expression of a transgene in a mouse is often not predictive of high expression in other species, including pigs and rabbits because, for example, the cis acting elements may interact with different trans-acting factors in these other species (paragraph bridging pages 238-239). While the instant claims are limited to transgenic mice, the unpredictability of phenotype due to species differences further demonstrates the level of unpredictability in the transgenic art. Even differences in the genetic background of transgenic mice can have an unpredictable effect on phenotype (Sigmund, 2000). Futhermore, the working examples in the instant specification do not demonstrate functional recombination in the transgenic mice of the claimed invention. Given the limited working examples, the existence of any phenotypic alteration resulting from the introduction of an Flp recombinase transgene is highly unpredictable. In view of the limited working examples and the unpredictability in the art, one skilled in the art would have been required to engage in undue experimentation in order to make and use the claimed transgenic mice.

The working examples demonstrate that recombination was detectable by Southern analysis (p. 40, paragraphs 2 and 3), but β-galactosidase activity was not detected (p. 45, paragraph 1). The specification states that:

> "Although all three FRTZ target lines analyzed here were competent for recombination, none of the recombined target alleles were sufficiently active to allow cell marking by XGal stain. The lack of βGal activity associated with the observed recombination most likely reflects a position effect on transgene transcription exerted by the genomic integration site since only one in four control *FRTZ-product* mouse lines expresses βGal." (p. 45, lines 9-14)

However, the specification goes on to state that "[i]mportantly, by screening additional FRTZ target loci, a chromosomal integration site has been identified that can support lacZ expression following Flp-recombination" (p. 45, lines 16-18). However, no further guidance is offered with regard to the critical element of producing functional recombination. The specification further reveals that in muscle, approximately 30% of the transgenes were in the recombined configuration as determined by Southern analysis (p. 40-41). The problems encountered with respect to producing functional recombination suggest either imprecise recombination, wherein recombination does not result in gene activation, or inefficient recombination, wherein gene inactivation is only partial. Thus, the specification does not demonstrate a phenotype produced by a deletion resulting in a null mutation because partial gene inactivation is not really a null mutation if only some cells have the deletion. Furthermore, the specification does not demonstrate a phenotype produced by insertion of a gene or activation of a gene as a consequence of deletion of a disrupting segment, because the specification does not teach how to produce functional recombination wherein the recombined gene is intact and functional.

With regard to Claim 1, the claim is not enabled because, in the absence of an Flp-recognition sequence, no recombination can occur. The specification does not teach how to use a transgenic mouse having only an Flp recombinase transgene but no Flp-recognition sites. In the absence of specific guidance, one skilled in the art would not know how to use an Flp recombinase transgenic mouse with no Flp-recognition sequences.

Applicants have offered the declaration of Dr. Hammer which states that his group had tried to produce Flp recombinase transgenic mice without success. Thus, Applicants argue that there is no expectation of success for making the claimed mice because others had tried and failed. The declaration leaves it unclear as to whether the method employed in the specification and declaration would be expected to

produce a functional recombination wherein the recombined gene is intact and functional. The declaration indicates that recombination did not occur or that it did not produce a functional gene. The experiments described in the specification are parallel to those described in the declaration of Dr. Hammer, but no recombination was detected in the experiments carried out by Dr. Hammer. Thus, it is left unclear as to whether the transgenic mice disclosed in the specification produce or can be expected to produce a functional gene upon recombination.

Applicants also argue that the claimed invention can be used for cell lineage marking and that cell lineage may be traced independent of gene activity. Furthermore, Applicants argue that chimerism in the number of Flp recombination sequences may be used to trace cell lineages. However, cell lineage marking is not a specific utility because any piece of DNA inserted into the genome can be used to trace cell lineage. Enablement is evaluated herein with respect to the utility disclosed in the specification, i.e. for gene activation or inactivation. While this is a credible utility, the specification is not enabling for this use. Applicants argue that functional recombination is not essential for the operability of the invention. However, there is not a specific and substantial utility for the invention when recombination produces a non-functional gene. Thus, functional recombination is essential to the operability of the invention.

Given the unpredictability in the transgenic art, the limited working examples with respect to gene activation or inactivation, and the limited guidance in the specification for producing functional recombination in the claimed transgenic mice, one skilled in the art would have been required to engage in undue experimentation to make and use the claimed compositions and methods.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Baker whose telephone number is (703) 306-9155. The examiner can normally be reached Monday through Thursday and alternate Fridays from 9:00 AM to 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen Hauda, can be reached on (703) 305-6608. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-8724.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Anne-Marie Baker, Ph.D.

Karen M. Hauda

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